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EXAMINER	
CHO, DAN SUNG C	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,403	SODERLUND ET AL.	
	Examiner	Art Unit	
	Dan-Sung C. Cho	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/4/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. This application is a 371 of PCT/FI03/00544 07/04/2003 and claims priority to FINLAND 20021325 07/05/2002.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1 and 19 recite "organized pools" in line 8 and line 2, respectively. It is unclear what constitutes organized pools. The specification defines pool as a mixture, or subset or a library of soluble or solubilizable polynucleotide probes in page 9, lines 7-9. The specification defines organized as related to being able to know the identity of the probe collection. However, it is not clear how a mixture of probes is organized.

b. Claims 1, 11, 17, and 29 recite "preset optional number" in lines 6, 2, 6 and 1-2, respectively. The term is indefinite because it is not clear what are the metes and bounds of the claims. It is not clear how and what is being optionally set at what number.

c. Claims 1 and 19 recite "approximately" in line 9 and line 6. The term is indefinite because it is not clear what are the metes and bounds of the claims.

d. Claims 1 and 14 recite “quantitative” and “quantitatively” in lines 3, 22, 23, 24, 26 and line 2, respectively. It is unclear how hybridization formation is quantitative or done quantitatively.

e. Claim 1 recites limitations “having approximately the same number of hybridizing nucleotides”. It is unclear the similar number of hybridizing nucleotides is in reference to probe length or actual number of nucleotides that form hybridization. It is also not clear if the similar number of nucleotides is within a pool or within a probe.

f. Claim 1 recites the limitation "the affinity pair" in line 25. There is insufficient antecedent basis for this limitation in the claim 1 the instant claim depends from.

g. Claims 2, 4 recite “dynamic” variations in lines 2. It is not clear how variations are dynamic. The metes and bounds of the claim are unclear. Claims 2 and 4 also recite “more or less” in lines 5 and line 6, respectively. It is not clear what are the metes and bounds of the claim.

h. Claim 4 recites the limitation "deoxyribonucleotide" in line 4. There is insufficient antecedent basis for this limitation in the claim 1 the instant claim depends from.

i. Claim 11 recites “more than one preferably more than five, most preferably more than ten”. It is not clear what are the metes and bounds of the claim.

j. Claim 14 recites the limitation "primer" in line 2. There is insufficient antecedent basis for this limitation in the claim 1 the instant claim depends from.

k. Claim 19 is indefinite because it is unclear whether the claims are drawn to a method of the use according to claim 1 of a test kit or a kit itself. The last step of the claimed method recites, "Characterized" in line 2; however, the active steps involved in the characterized are not defined.

l. Claims 19-35 provide for the use of a kit, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 19-35 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1, 5-13, 16, 19, 21, 23-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leying (Leying et al., Oct., 2000, US Patent 6136531) in view of Grossman (Grossman et al., Sep., 1998, US Patent 5807682).

With regard to claim 1, and 19, Leying teaches a method of quantitatively detecting specific nucleotide sequences via solution hybridization and subsequent immobilization of hybrids on a solid phase (Abstract). With regard to claim 1(a), Leying teaches providing mRNA population that is labeled with biotin (col. 5, EXAMPLE 3) to a set of probes, each complementary to target RNA sequences of actin and CAT (col. 5, EXAMPLE 2). The probe length for actin is 838 bp and CAT, 367 bp (col. 5, EXAMPLE 1). Leying teaches probes are labeled with DIG-dUTP (col. 5, EXAMPLE 1) that is subsequently detected to determine the quantity of the RNA hybridized to the probes by recording the amount of actin and CAT RNA specific numbers with anti-DIG-POD antibody (col. 6, lines 11-14; Table 1). The DIG labeling of the probes did not disturb hybridization as evidenced by the successful detection and quantification of each RNA

with the probes labeled with DIG (Table 1). With regard to claim 1(b), Leying teaches providing analyte polynucleotide sequences isolated form HeLa cells (col. 5, EXAMPLES 2 and 3) and labeling with an affinity tag, biotin (col. 5, EXAMPLE 3). With regard to claim 1(c), Leying teaches performing steps (i) hybridization between the probes and analytes in the sample to form soluble hybrids (col. 6, lines 1-9). The probe used was 4 μl of 20 ng/μl or 80 ng and samples of analytes, which is total RNA and comprised of many different RNAs, was about 2-600 ng. For example, when 37.5 ng total RNA was used with a molar excess amount of 80 ng probe to detect the relative amounts of CAT RNAs which was twice as much in the sample prepared from CAT-transfected cells than non-transfected as expected (Table 1). With regard to claim 1(c)(ii), Leying teaches performing steps to recover hybrids via tBSA-SA plate (col. 6, line 7).

With regard to claim 21, Leying teaches that the analytes are isolated from the sample comprising mRNAs (col. 5, Example 3).

With regard to claims 5 and 23, Leying teaches that the analytes are total mRNA isolated from Hela cells (col. 5, Examples 2-3) which would contain ribosomal RNA.

With regard to claims 6 and 24, Leying teaches a method wherein DIG label is used as tracer for chemiluminescent detection of the target. The DIG label also acts as an affinity tag because the anti-DIG antibody has specific affinity for the DIG label and binds specifically to the probe labeled with DIG (Figure 7).

With regard to claims 7 and 25, Leying teaches a method wherein the resolution enabling tag for the probe is DIG-dUTP (col. 5, EXAMPLE 2) which when incorporated into a nucleic acid can be separated in a sieving medium such as an acrylamide gel.

With regard to claims 8, and 26, Leying teaches a method wherein DIG label is used as tracer for chemiluminescent detection of the target and also acts as an affinity tag because the anti-DIG antibody has specific affinity for the DIG label and binds specifically to the probe labeled with DIG (Figure 7). Leying teaches that DIG-dUTP is incorporated into probes and is an oligonucleotide residue within the probe sequence (col. 5, EXAMPLE 1).

With regard to claims 9 and 27, Specification teaches that peptide oligonucleotide conjugates as an example of amino acids and peptides that can be used as a tag on page 11, lines 8-11). Therefore the instant claims are broadly interpreted as encompassing a polypeptide bond containing nucleic acid molecules. Leying teaches a method wherein the tag is on peptide nucleic acid (PNA) and that PNA hybridizes to RNA sample more efficiently (col. 2, lines 53-61).

With regard to claims 10 and 28, Leying teaches a method wherein the tag (col. 5, EXAMPLE 1) is DIG-dUTP which is detected by anti-DIG/POD antibody whose POD enzymatic activity in turn is recorded (col. 5, lines 5-15; Table 1), spectrometrically with a Microplate Luminometer LP 96P that automatically integrates and records detected signals (col., 5, lines 15-17).

With regard to claims 11 and 29, Leying teaches a method wherein two different soluble polynucleotide probes for actin and CAT are used (col. 5, EXAMPLE 1 line 6).

With regard to claims 12 and 13, Leying teaches a method wherein the detection of labeled probes that were bound and released is recorded spectrometrically with a Microplate Luminometer LP 96P which automatically integrates and records detected signals (col., 5, lines 15-17).

With regard to claims 16 and 31, Leying teaches a method wherein DIG labeled PCR amplified probes are used (col. 5, EXAMPLE 1).

With regard to claim 30, Leying teaches a method wherein DIG labeled PCR amplified probes are detected in tBSA-SA plate wells (col. 6, line 7 and Table 1, "ng/well" reference).

Leying does not teach a method wherein step (a) the probes have approximately same number of hybridizing nucleotides; (d) quantitatively releasing the polynucleotide probes in an unmodified form from the hybrids captured; and step (e) separating and recording the amount or relative proportions of probes wherein the amount of the probes corresponds to the amount of the target RNA in the sample.

However, with regard to claim 1(a), Grossman teaches a method of target polynucleotide detection wherein the different sequence probes that are used to hybridize to complementary sequences in a sample all have about the same length, allowing hybridization of the different probes to the target with substantially same hybridization kinetics and thermodynamics (col. 7, lines 1-5). With regard to claim 1(d), Grossman teaches a method wherein the bound probes are released in an unmodified form by breaking the hydrogen bonds between the probes and the target RNAs (col. 20,

lines 53-58). With regard to claim 1(e), Grossman teaches a method wherein the released probes are fractionated by capillary electroporation and identify target sequences on the basis of distinctive electrophoretic positions of the fractionated labeled probes (col 11, lines 45-65; col. 20, lines 55-58). Electrophoregram of fractionated labeled probes have areas for each probe peak, the area under which each peak corresponds to the amount of the target RNA (See Figure 9, for example). Grossman teaches that capillary electrophoresis method can fractionate probes of similar sizes, and thus similar hybridization conditions (col. 12, lines 1-10).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method wherein the probes Leying taught to have similar nucleotide size in step 1(a); releasing the polynucleotide probes in an unmodified form from the hybrids captured in step 1(d); and separating and recording the amount or relative proportions of probes wherein the amount of the probes corresponds to the amount of the target RNA in the sample in step 1(e) as taught by Grossman. The ordinary artisan would be motivated to include similarly sized probes in step 1(a) because Grossman teaches that similar length probes allow hybridization of the different probes to the target with substantially same hybridization kinetics and thermodynamics (col. 7, lines 1-5). The ordinary artisan would be motivated to further release the probes in an unmodified in step 1(d) and separate and record the amount or relative proportions of probes that corresponds to the amount of the target RNA in the sample in step 1(e) as taught by Grossman because electrophoregram of

fractionated labeled probes obtained corresponds to the amount of the target RNA in the sample (See Figure 9, for example).

5. Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leying, Grossman as applied to claim 1 above, and further in view of in view of in view of Chen-Liu (Chen-Liu et al., 1995, Genomics 30: 388-392).

The teachings of Leying and Grossman as applied to claim 1 are as set forth above.

Leying and Grossman do not teach a method of wherein released probes are amplified by PCR and recorded with a recording system based in the resolution enabling tags in claim 14 and wherein the primer is a universal primer in claim 15.

However, Chen-Liu teaches a method of PCR amplifying a microdissected chromosome 11 with a universal primer (page 389, left col., lines 13-19). Chen-Liu teaches that the universal primer-mediated PCR amplification and labeling enables specific detection of the target DNA by subsequent FISH or Dot blot analyses wherein the target sequence detection is recorded with a recoding systems selected based on the resolution on the resolution enabling tags (Figures 1 and 2). Chen-Liu teaches that the method of amplifying probes results in enrichment of the target sequences (page 390, left col., line 1).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of using probes of Leying and Grossman wherein the released probes are amplified by universal primer and

labeled thereby enabling detection of the target with a recording system as taught by Chen-Liu. One of ordinary skill in the art would have been motivated to modify the use of probe to include a universal primer sequence and record the PCR amplicons with a recording system selected based in the resolution enabling tags as taught by Chen-Liu to enrich the target sequences thereby enabling detection of rare target sequence.

6. Claims 2-4, 17, 20, 22, 32 and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leying and Grossman as applied to claims 1, 5-13, 16, 19, 21, 23-31 above, and further in view of in view of Amann (Amann et al., 1990, Applied and Environ Microbiol, 56: 1919-1925).

The teachings of Leying and Grossman as applied to claims 1, 5-13, 16, 19, 21, 23-31 are as set forth above.

Leying and Grossman do not teach a method of selecting probes from conserved or hypervariable regions from intragenic region sequences for subgroups, species subspecies of transcripts expressed in the organism in claims 2 and 20; wherein the mixed target RNA is mRNA or rRNA in claims 3 and 5; and probes are designed for determination of variations in the amounts or relative proportions of polynucleotide sequences comprising the mixed target populations in claim 4, 22; and wherein test kits of probes used to determine comparative, quantitative assessment of variations in the amounts of organisms are used in claims 17 and 32; use of a kit for assessing hygienic conditions and epidemiologic situations in claims 34 and 35.

However, with regard to claims 2 and 20, Amman teaches a method wherein about probes are designed from species or group-specific ribonucleotide sequences with conserved or hypervariable regions from intragenomic rRNA sequences specific for subgroups, species subspecies of transcripts expressed in the organism, such as the eubacterial probe, specific for all eubacteria; sulfate-reducing bacteria (SRB) probe, specific for most species of the δ–group of purple bacteria; and desulfobacter probe, specific for the genus Desulfobacter; and eukaryotic probe, specific for eukaryotes (page 1920, left col., para 2). Amann teaches use of the probes to detect and enumerate specific cells in mixtures of D. gigas and E. coli cells were made to give final concentrations of D. gigas of 50, 20, 3 and 0.8% of the total cell number (page 1922, left col., last para to right col., para 1).

With regard to claims 3 and 5, Amann teaches a method wherein the probes are used to hybridize to fixed cells of mixed populations thereby exposing analytes including mRNA and rRNA to the probes for specific hybridization (page 1921, left col., para 1).

With regard to claims 4 and 22, Amann teaches a method wherein the DNA probes are designed from group or species specific RNA sequences that represent different phylogenetic levels, eukaryotes, eubacteria, sulfate-reducing bacteria, Desulfobacter in a mixed target population (page 1920, left col., para 2; page 1922, right col., para 2).

With regard to claims 17 and 32, Amann teaches a method wherein the species and subgroup and group specific probes are used to determine the comparative quantitative assessment of various amounts of individual organisms of D. gigas and E.

coli cells (page 1922, right col., lines 9-15). Amann teaches a method wherein a bitmap analysis of the flow cytometric detection of the mixed populations is used to assess the mixed population cell counts (page 1922, right col., para 2) with the identical purified probes (page 1921, left col., lines 1-6). A test kit is defined as comprising of one or more polynucleotide probes in the specification on page 24, para 4). Therefore the instant claim is given the broadest reasonable interpretation to encompass polynucleotide probes which are taught by Amann.

With regard to claims 34 and 35, although Amann does not specifically teach a use of probes for assessing hygienic conditions and epidemiologic situations, because Amann teaches that the probes can detect any the method of using different rRNA probes permits detection and identification of virtually any microorganism (page 1920, left col., para 1, lines 10-11) and track population changes (page 1923, right col., last sentence), Amann teaches use of probes for assessing hygienic conditions and epidemiologic situations, including treatment with antibiotics or hygienic measures.

Amman teaches that the specificity of probes against selected regions within the larger rRNA such as16S can be freely adjusted to distinguish microbial species and subspecies or simultaneously detect genera, or higher phylogenetic taxons to measure total abundance in the environment and to assess difference in cellular rRNA content (page 1919, left col., para 2), permitting detection and identification of virtually any microorganism (page 1920, left col., para 1, lines 10-11) and track population changes (page 1923, right col., last sentence).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Leying and Grossman wherein the probes are replaced with probes selected from conserved or hypervariable regions from intragenic region sequences of mRNA or rRNA of group or species specific probes for determination of variations in the amounts or relative proportions of polynucleotide sequences comprising the mixed target populations and using test kits of probes to determine comparative, quantitative assessment of variations in the amounts of organisms for assessing hygienic conditions and epidemiologic situations as taught by Amman.

The ordinary artisan would be motivated to replace the probes of conserved or hypervariable region sequences of mRNA or rRNA for determination of variations in the amounts or relative proportions of mixed target populations and using test kits of probes to determine comparative, quantitative assessment of variations in the amounts of organisms for assessing hygienic conditions and epidemiologic situations in claims 34 and 35.as taught by Amman because Amman teaches such probes permit detection and identification of virtually any microorganism in a sample (page 1920, left col., para 1, lines 10-11) and track population changes (page 1923, right col., last sentence).

7. Claims 18 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leying, Grossman and Amann as applied to claims 1, 17, 19 and 32 above, and further in view of in view of in view of Strathmann (US 6480791).

The teachings of Leying, Grossman and Amann as applied to claims 1, 17, 19 and 32 are as set forth above.

Leying, Grossman and Amann do not teach a method of wherein a set of multiple test kits is provided with tracer tags each being distinguishable from the other by the emitted signal.

However, Strathmann teaches a method of labeling probes with fluorescent tags such as fluorescent, rhodamines and quantum dots to facilitate detection (col., 35, lines 10-15) thereby facilitating detection of target nucleic acids (col., 35, lines 10-15).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of using probes of Leying, Grossman and Amann by labeling probes with fluorescent labels in test kits that are distinguishable from each other as taught by Strathmann. One of ordinary skill in the art would have been motivated to use a method of labeling probes with distinguishable fluorescent labels in test kits as taught by Strathmann to detect target analytes simultaneously.

Conclusion

8. No claims allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Dan-Sung C. Cho whose telephone number is (571) 272-9933. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

Dan-Sung C. Cho
Examiner
AU1634

JEHANNE SITTON
PRIMARY EXAMINER
4/2/07